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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/330,903	06/11/1999	IGOR GONDA	6513/061US1	9995

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/330,903	GONDA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-60 and 70-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-60 and 70-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment after final was received and entered on 2/13/06.

The declaration of Dr. Gonda under 35 USC 131 was sufficient to overcome the rejections under 35 USC 103. Applicant's amendments were sufficient to overcome the rejections of claims 64 and 73 for indefiniteness.

Finality of the previous Office Action is withdrawn, and prosecution is reopened in light of the following new grounds of rejection.

Claims 58-64 and 66-73 are pending and under consideration in this Office Action.

Priority

It is noted that this application claims priority to US Patent Application 08/752,946 (US Patent 5,906,202), however, the relationship between the prior application and the instant application is not disclosed. For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. See 37 CFR 1.78(a). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58-64 and 66-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 58-64 and 66-73 are indefinite because they recite "the patient's inhaled volume" without antecedent basis. The claims recite no step in which inhalation occurs.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 58-62 and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Debs (US Patent 5,756,353).

Debs taught a method of delivering condensed polynucleotides in aerosol particles to a target region in the lung by adjusting the size of the particles to target specific lung regions. The polynucleotides were condensed by cationic lipids in lipid compositions that comprised negatively charged lipids such as phosphatidyl glycerol, or neutral lipids comprising a negative charge, such as phosphatidyl ethanolamine. See claim 8. A size range of from 0.5-5 microns is suggested for alveoli, and a size range of 4-12 microns is suggested for airway delivery. See column 12, lines 51-56, 60, and 61; and claims 1, and 14-16. Because Debs teaches size ranges overlapping the instantly claimed ranges, Debs teaches particles within each of the instantly claimed ranges, and

so delivery to the instantly claimed sites is considered to be inherent. The volume of aerosol-containing air and aerosol-free air is controlled by the particular administration device used. See column 12, line 25 to column 13, line 43. The particular characteristics of a nebulizer will inherently determine how much, if any, aerosol-free air is admitted during inspiration of the aerosol, as well as the amount of aerosol-containing air that can be inhaled.

Thus Debs anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 58-62 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debs (US Patent 5,756,353) in view of Jaser et al (US Patent 5,458,136).

Debs anticipates claims 58-62 and 72 for the reasons set forth above. This rejection is directed to an embodiment of the claimed invention which would require inhalation of both aerosol-free air and aerosol-containing air.

Debs taught a method of delivering condensed polynucleotides in aerosol particles to a target region in the lung by adjusting the size of the particles to target specific lung regions. The polynucleotides were condensed by cationic lipids in lipid compositions that comprised negatively charged lipids such as phosphatidyl glycerol, or

neutral lipids comprising a negative charge, such as phosphatidyl choline. See claim 8. A size range of from 0.5-5 microns is suggested for alveoli, and a size range of 4-12 microns is suggested for airway delivery. See column 12, lines 51-56, 60, and 61; and claims 1, and 14-16. Because Debs teaches size ranges overlapping the instantly claimed ranges, Debs teaches particles within each of the instantly claimed ranges, and so delivery to the instantly claimed sites is considered to be inherent.

Jaser taught a device that allowed inhalation of distinct volumes of aerosol-free air and aerosol containing air within a single inspiratory cycle, allowing delivery of sharply defined pulses of aerosol. See column 1, lines 42-54, and column 2, lines 24-40.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the device of Jaser to deliver the aerosol of Debs. One would have been motivated to do so because Jaser taught that deposition of an aerosolized drug in desired lung areas is improved if the aerosol is delivered in sharply defined pulses. See column 1, lines 7-11 and column 2, lines 24-27. Thus the invention as a whole was prima facie obvious.

Claims 63, 67-69, and 72, are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al (US Patent 5,795,587) in view of Debs (US Patent 5,756,353) and Jaser et al (US Patent 5,458,136).

Gao taught stable lipid-comprising nucleic acid delivery particles in which the nucleic acid is complexed with polycations and lipids. See column 9, line 40 to column

10 line 11, especially column 10, lines 6-11. See also claims 4 and 11. The particles may be delivered as an aerosol. See column 11, lines 30-34. The polycation may be a polyamine such as polylysine, protamines, spermine, or spermidine. See column 9, lines 40-53. The complexes may contain negatively charged lipids such as phosphatidyl glycerol, or neutral lipids comprising a negative charge, such as phosphatidyl choline. See column 8, lines 35-50.

Gao did not teach controlling the aerodynamic diameter of the aerosol particles to influence the site of delivery in the lung, or controlling the volume of inhaled aerosol or aerosol-free air.

Debs taught a method of delivering condensed polynucleotides in aerosol particles to a target region in the lung by adjusting the size of the particles to target specific lung regions. A size range of from 0.5-5 microns is suggested for alveoli, and a size range of 4-12 microns is suggested for airway delivery. See column 12, lines 51-56, 60, and 61; and claims 1, and 14-16.

Jaser taught a device that allowed inhalation of distinct volumes of aerosol-free air and aerosol containing air within a single inspiratory cycle, allowing delivery of sharply defined pulses of aerosol. See column 1, lines 42-54, and column 2, lines 24-40.

It would have been obvious to one of ordinary skill in the art at the time of the invention to control both the particle size of the aerosol and the volumes of inhaled aerosol-containing and aerosol-free air in view of the teachings of Debs and Jaser. One

would have been motivated to do so in order to target specific sites in the lungs as taught by Debs and Jaser.

Thus the invention as a whole was prima facie obvious.

Claims 64 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al (US Patent 5,795,587), Debs (US Patent 5,756,353), and Jaser et al (US Patent 5,458,136) as applied to claims 63, 67-69, and 72 above, and further in view of Birnstiel et al (US Patent 5,922,859).

The teachings of Gao, Debs, and Jaser are discussed above and can be combined to render obvious a method of delivering to a target site in a lung, aerosolized particles comprising a polycation-condensed nucleic acids and negatively charged lipids, wherein the aerodynamic diameter of the particles has been adjusted to target a specific site, and wherein the volumes of aerosol-free and aerosol-containing air are controlled.

Although these references taught condensing polynucleotides with protamine, they did not specifically teach protamine sulfate.

Birnstiel taught that protamine sulfate a functional equivalent to polylysine and histones for DNA condensation, and could be substituted for, or combined with, these other polycations in nucleic acid delivery compositions. See paragraph bridging columns 18 and 19, and Table I at column 27. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An

express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the prior art clearly considered protamines, including protamine sulfate to be equivalent to other polycations as a nucleic acid condensing agent. Regarding column 64, the size to which protamine sulfate condenses polynucleotides is considered to be an inherent characteristic of protamine sulfate.

Thus the invention as a whole was prima facie obvious.

Claims 68 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al (US Patent 5,795,587), in view of Debs (US Patent 5,756,353), Jaser et al (US Patent 5,458,136) and Chu et al (US Patent 6,030,834, issued 2/29/00).

The teachings of Gao, Debs, and Jaser are discussed above and can be combined to render obvious a method of delivering to a target site in a lung, aerosolized particles comprising a polycation-condensed nucleic acids and negatively charged lipids, wherein the aerodynamic diameter of the particles has been adjusted to target a specific site, and wherein the volumes of aerosol-free and aerosol-containing air are controlled.

Although these references taught condensing polynucleotides with polyarginine, polyornithine, protamines and polylysine, polybrene (hexadimethrine bromide), histone, cationic dendrimer, spermine, and spermidine (See Gao at column 9, lines 40-53) , they did not specifically teach putrescine as a polycation nucleic acid condensing agent.

Chu taught that polycationic condensing agents include polylysine, polyarginine, polyornithine, protamine, spermine, spermidine, and putrescine. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the prior art clearly considered putrescine to be equivalent to protamine, spermine, and spermidine as a nucleic acid condensing agent.

Thus the invention as a whole was prima facie obvious.

Claims 69 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al (US Patent 5,795,587), in view of Debs (US Patent 5,756,353), Jaser et al (US Patent 5,458,136), and Curiel et al (US Patent 5,547,932, issued 8/20/96).

The teachings of Gao, Debs, and Jaser are discussed above and can be combined to render obvious a method of delivering to a target site in a lung, aerosolized particles comprising a polycation-condensed nucleic acids and negatively charged lipids, wherein the aerodynamic diameter of the particles has been adjusted to target a specific site, and wherein the volumes of aerosol-free and aerosol-containing air are controlled.

Although these references taught condensing polynucleotides with polyarginine, polyornithine, protamines and polylysine, polybrene (hexadimethrine bromide), histone, cationic dendrimer, spermine, and spermidine (See Gao at column 9, lines 40-53) , they did not specifically teach putrescine as a polycation nucleic acid condensing agent.

Curiel taught the use of polylysine, polyethyleneimine, protamine, spermine, and spermidine as DNA condensing agents, as well as the subsequent delivery of the condensed DNA to lung tissue by aerosol administration. See column 25, lines 21-32, and column 36, lines 6-17. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the prior art clearly considered

polyethyleneimine to be equivalent to polylysine, protamine, spermine, and spermidine as a nucleic acid condensing agent.

Thus the invention as a whole was prima facie obvious.

Claims 70 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al (US Patent 5,795,587), Debs (US Patent 5,756,353), and Jaser et al (US Patent 5,458,136) as applied to claims 63, 67-69, and 72 above, and further in view of Cooper (US Patent 5,474,059)

The teachings of Gao, Debs, and Jaser are discussed above and can be combined to render obvious a method of delivering to a target site in a lung, aerosolized particles comprising a polycation-condensed nucleic acids and negatively charged lipids, wherein the aerodynamic diameter of the particles has been adjusted to target a specific site, and wherein the volumes of aerosol-free and aerosol-containing air are controlled.

These references do not indicate any preferred inspiratory flow rate for particle deposition.

Cooper taught that it was routine for patients inhaling aerosol medications to vary their inspiratory flow rate in a range of 30-120 liters/minute, corresponding to 0.5-2 liters/second. This rate is within the instantly claimed range of 0.2-3.0 liters per second. Cooper also taught that the inspiratory flow rate affected the deposition profile of the aerosol particles. See column 3, lines 1-6. As a result it would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the inspiration flow

rate when delivering ay aerosol composition, and it would have been obvious to do so within the instantly claimed range.

Conclusion

No claim is allowed. Claim 66 is free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635

DETAILED ACTION

An amendment was received and entered on 9/6/06.

Claims 61-64 and 73 were canceled.

Claims 58-60 and 70-72 remain pending and are under consideration.

Applicant's amendments overcame the previous rejection of claims 58-60 and 70-72 for indefiniteness.

Rejections not reiterated from the previous Action are withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 58-60 and 72, are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al (US Patent 5,795,587) in view of Debs (US Patent 5,756,353), Jaser et al (US Patent 5,458,136), and Birnstiel et al (US Patent 5,922,859).

Gao taught stable lipid-comprising nucleic acid delivery particles in which the nucleic acid is complexed with polycations and lipids. See column 9, line 40 to column 10 line 11, especially column 10, lines 6-11. See also claims 4 and 11. The particles may be delivered as an aerosol. See column 11, lines 30-34. The polycation may be a polyamine such as polylysine, protamines, spermine, or spermidine. See column 9,

lines 40-53. The complexes may contain negatively charged lipids such as phosphatidyl glycerol, or neutral lipids comprising a negative charge, such as phosphatidyl choline. See column 8, lines 35-50.

Gao did not teach controlling the aerodynamic diameter of the aerosol particles to influence the site of delivery in the lung, controlling the volume of inhaled aerosol or aerosol-free air, and although these references taught condensing polynucleotides with protamine, they did not specifically teach protamine sulfate.

Debs taught a method of delivering condensed polynucleotides in aerosol particles to a target region in the lung by adjusting the size of the particles to target specific lung regions. A size range of from 0.5-5 microns is suggested for alveoli, and a size range of 4-12 microns is suggested for airway delivery. See column 12, lines 51-56, 60, and 61; and claims 1, and 14-16.

Jaser taught a device that allowed inhalation of distinct volumes of aerosol-free air and aerosol containing air within a single inspiratory cycle, allowing delivery of sharply defined pulses of aerosol. The sharp definition of the pulse is essential for the therapeutic or diagnostic application of aerosol pulses which are injected into the patient's breathed air during deep inspiration. For therapy, the effective substance in the aerosol pulse can only be deposited in the desired lung areas if the aerosol pulse is very distinct. See column 1, lines 6-12, and 42-54; and column 2, lines 24-40.

It would have been obvious to one of ordinary skill in the art at the time of the invention to control both the particle size of the aerosol and the volumes of inhaled aerosol-containing and aerosol-free air in view of the teachings of Debs and Jaser. One

would have been motivated to do so in order to target specific sites in the lungs as taught by Debs and Jaser.

Birnstiel taught that protamine sulfate is a functional equivalent to polylysine and histones for DNA condensation, and could be substituted for, or combined with, these other polycations in nucleic acid delivery compositions. See paragraph bridging columns 18 and 19, and Table I at column 27. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the prior art clearly considered protamines, including protamine sulfate to be equivalent to other polycations as a nucleic acid condensing agent. The size to which protamine sulfate condenses polynucleotides is considered to be an inherent characteristic of protamine sulfate.

Thus the invention as a whole was prima facie obvious.

Claims 70 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al (US Patent 5,795,587), Debs (US Patent 5,756,353), Jaser et al (US

Patent 5,458,136), and Birnstiel et al (US Patent 5,922,859) as applied to claims 58-60 and 72 above, and further in view of Cooper (US Patent 5,474,059)

The teachings of Gao, Debs, Jaser, and Birnstiel are discussed above and can be combined to render obvious a method of delivering to a target site in a lung, aerosolized particles comprising a protamine sulfate-condensed nucleic acids and negatively charged lipids, wherein the aerodynamic diameter of the particles has been adjusted to target a specific site, and wherein the volumes of aerosol-free and aerosol-containing air are controlled.

These references do not indicate any preferred inspiratory flow rate for particle deposition.

Cooper taught that it was routine for patients inhaling aerosol medications to vary their inspiratory flow rate in a range of 30-120 liters/minute, corresponding to 0.5-2.0 liters/second. This rate is within the instantly claimed range of 0.2-3.0 liters per second. Cooper also taught that the inspiratory flow rate affected the deposition profile of the aerosol particles. See column 3, lines 1-6.

It would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the inspiration flow rate when delivering any aerosol composition because Cooper showed that inspirational flow rate was a result effective variable. It would have been obvious to do so within the instantly claimed range because Cooper taught that it was routine for patients inhaling aerosol medications to vary their inspiratory flow rate in a range of 30-120 liters/minute, corresponding to 0.5-2.0 liters/second.

Response to Arguments

Applicant's arguments filed 9/6/06 have been fully considered but they are not persuasive.

Applicant addresses the rejections at pages 6 and 7 of the response. Applicant alleges that the rejections were only made by utilizing Applicant's specification as a blueprint for combining the references. This is unpersuasive because it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Applicant has not persuasively identified any knowledge that was gleaned only from the instant disclosure and was not available in the cited art.

Applicant argues that Debs teaches nebulizer technology that does not allow one to control a patient's inhaled volume of aerosol, and so is not properly combinable with Jaser. This is unpersuasive because Jaser taught that sharp definition of an aerosol pulse is essential for the therapeutic or diagnostic application of aerosol pulses which are injected into the patient's breathed air during deep inspiration. For therapy, the effective substance in the aerosol pulse can only be deposited in the desired lung areas if the aerosol pulse is very distinct. See column 1, lines 6-12. Thus, there was a clear advantage in modifying the nebulizer teachings of Debs according to Jaser.

Applicant argues that the combination of references is not teaching toward the condensation of polynucleotides into a particular size range and the direction of aerosolized particles to a particular area of the lung. This is unpersuasive. The primary reference teaches aerosol delivery of polynucleotides condensed with polycation condensing agents, including protamine. Absent evidence to the contrary, the size of a particular polycation/ polynucleotide complex is inherently dictated by the structure of the polycation and the polynucleotide. Tang et al (Gene Therapy, 4: 832-832, 1997, of record) taught that cationic nucleic acid condensing agents with diverse structures such as such as polylysine, polyethyleneimine, and fractured or intact polyamidoamine dendrimers, form toroidal particles on the order of about 20-80 nm when complexed with DNA plasmids, with the majority of particles being 43-67 nm. See abstract and Fig. 4 on page 832. In view of the teachings of Tang, polycations generally give DNA complexes in the range of 20-80 nm. Absent evidence to the contrary, protamine sulfate condenses DNA to a size in this range as well. So, the primary reference effectively teaches condensation of polynucleotides into a particular size range and administration of aerosolized particles to the lung. Similarly, Debs taught a method of delivering condensed polynucleotides in aerosol particles the lung, but improved the method by targeting specific lung regions by adjusting the size of the particles. Therefore it was routine in the art at the time of the invention to target aerosolized condensed polynucleotides to particular lung sites by controlling the size of the inhaled aerosol particles, and it was routine to condense polynucleotides for aerosolized delivery to the lungs with a variety of condensing agents including protamine. The

method of Debs improves the method of Guo by allowing one to target a specific area of the lung, and the invention of Jaser improves on the method of Debs by improving the specificity of targeting. Addition of the Birnstiel reference simply makes clear that, in the event that the protamine of Gao was not a protamine sulfate, protamine sulfate was an art recognized equivalent of the DNA condensing agents used by Gau. Accordingly it would have been obvious to use it in the invention of Gao as modified by Debs and Jaser. For these reasons the rejections are considered proper.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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